REMARKS

Favorable reconsideration of the subject application, as amended above, is respectfully requested in view of the comments below.

Claims 1-5, 7-14, 16-18 and 20-24 are pending in the application. Claims 1 and 20 have been amended to more particularly define the protein that is detected and whose presence or amount is correlated with treatment effectiveness, *i.e.*, an intact modified form of the protein. Support for this amendment is provided throughout the specification and in the original claims. The language of Claims 2 and 13 has been amended to more particularly define the claimed invention. Claims 8, 18 and 24 are cancelled herein. New claims 25 and 26 are directed to an embodiment of the invention wherein immunoreactive and/or immuno-nonreactive forms of a protein are detected in a urine sample and their amount over time is correlated to therapeutic effect. These claims are supported throughout the specification, and in particular at page 10, where it is disclosed that certain forms of kidney filtered proteins are not detectable by radioimmunoassays using antibodies. Thus, these proteins are immuno-nonreactive.

I. Claim Objections

Typographical errors and omission of an explanation for an acronym in claim 2 have been corrected, rendering the formal grounds of objection to claim 2 moot.

II. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 13, 14, 18 and 24 are rejected under 35 U.S.C. § 112, second paragraph. The Examiner states that it is not understood how surgery qualifies as a "condition." In response, the

claim has been amended to more particularly recite "side effect of surgery," which is "condition."

The Examiner also asserts that "drug abuse" is a relative term. However, as shown by the definition provided by Stedman's Medical Dictionary (copy of relevant pages enclosed), the term is art accepted and means "habitual use of drugs not needed for therapeutic purposes." Thus, this term is not indefinite and its use in claim 2 meets the requirements of 35 U.S.C. § 112.

The term "lymphoreticular" has been corrected to recite "lymphoreticular disease" and the term "conventional" has been deleted from claim 13.

Accordingly, the rejection of claims 2, 13, 14, 18 and 24 under 35 U.S.C. § 112, second paragraph is respectfully traversed.

III. Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 1-5, 7-14, 16-18 and 20-24 stand rejected under 35 U.S.C. § 102(b) as anticipated by Trevesan *et al.* The Examiner speculates that the method disclosed by the cited reference may inherently detect intact modified protein. The Examiner concludes, therefore, that the claimed invention is anticipated.

This rejection is respectfully traversed as follows.

In the present invention, intact modified protein is specifically detected in urine samples of a patient undergoing therapy, and the amount of intact modified protein detected is correlated to the effectiveness of therapy. As a result, the present invention provides a very sensitive method for detecting a shift in protein content of urine, which enables accurate determination of the effectiveness of a particular therapy in reducing protein content in urine. As taught in the specification, in patients with kidney disease an increasing amount of modified albumin is first

detected in the urine, followed by an increase in native albumin. Thus, using the claimed method, the physician can detect the need for therapy at an earlier stage of the disease and can accurately assess progress of treatment at an earlier stage in the disease by monitoring intact modified proteins, which are generally not detectable by radioimmunoassays.

In contrast, Trevesan teaches a method of detecting albumin in urine by radiommunoassay (and only by radioimmune assay), but does not teach or suggest that urine contains intact modified forms of albumin and does not teach or suggest a method for detecting modified protein in urine. Consequently, this reference does not disclose or suggest detection of modified urinary albumin as an indicator of therapy progression. Instead, Trevesan uses conventional radioimmunoassay to detect albumin, which may or may not be capable of detecting any modified form of albumin, but as discussed in the inventor's declaration enclosed herewith, cannot detect all forms of intact modified albumin.

The antibody used by Trevesan was made to serum albumin, not urinary albumin. Trevesan cites to Christiansen *et al.* (Nephropathy 1984, 3:92-94) for description of the RIA used in the experiments disclosed therein. Christiansen describes the use of rabbit IgG to human serum albumin. Further, as stated in the enclosed declaration, the present inventor is aware of no publication or describing production or use of antibodies raised to urinary albumin, or the use of such antibodies to measure or detect urinary albumin. Consequently, even if Trevesan's anti-human serum albumin antibody detects some intact modified albumin, it is not capable of measuring the total amount of intact modified albumin and correlating amount thereof to efficacy of treatment.

As evidenced by the labeling of applicant's FDA-approved product, Accumin™, the FDA has recognized that immunoassays do not detect all intact albumin in urine. The FDA-approved label on Accumin™ states the following: "*Note: The Accumin™ HPLC assay detects albumin based on size exclusion chromatography calibrated by human serum albumin standard. The size-exclusion HPLC technology employed by the* Accumin™ HPLC assay *permits a direct measurement of albumin, regardless of the reactivity potential of the protein with antibodies. Since immunoassays (and dye binding assays) may not detect all of the intact albumin in urine samples it is expected that the HPLC technology employed by the* Accumin™ *HPLC* assay *will, depending on the specimen, report greater urinary albumin values when compared to immunochemical urinary albumin test systems and dipstick system. This trend has been observed at lower excretion rates, sometimes up to 100 μg/min in urine samples from diabetic patients.*"

As further evidence that RIA does not detect modified urinary albumin, Applicant encloses herewith a copy of a peer reviewed journal article (Osicka and Comper, Clinical Chemistry (2004) 50:1-6) that discusses the two types of urinary albumin – immunoreactive albumin, which is detected by RIA, and immunounreactive albumin, which is not detected by RIA. This paper also

Thus, it is known in the art that radioimmuneassays (RIA) detect significantly less urinary albumin than HPLC, and that urinary albumin exists in two forms- immunoreactive and immuno non-reactive. Dr. Comper's studies clearly demonstrate that RIA considerably underestimates urinary albumin excretion, particularly for excretion rates less than 100 μg/min. It is in this range that early diagnosis of kidney disease is made. Thus, the methodology

disclosed by Trevisan is not applicable to all stages of kidney disease, being limited instead to later stages when urinary albumin is detectable and therefore, can be tracked during treatment.

In contrast, Applicant has discovered the presence of immunonon-reactive protein in urine and has determined the significance of such materials in the diagnosis and treatment of disease. Because the present methods measure intact modified forms of protein, treatment can be started and tracked at a significantly earlier stage in disease.

Moreover, claims 9-14, 16 and 17 include a step of determining amount of protein by a method in addition to or in place of an antibody-based method so that the claimed method detects intact modified protein. Trevisan discloses only the use of RIA, and therefore, this reference clearly does not anticipate this subset of claims. Further, because Trevisan does not disclose or suggest the existence of immunounreactive proteins, it does not render the present claims obvious.

Accordingly, the rejection of claims 1-5, 7-14, 16-18 and 20-24 under 35 U.S.C. § 102(b) as anticipated by Trevesan *et al* .is respectfully traversed.

IV. Rejection of Claims Under 35 U.S.C. § 103(a)

Cancellation of claims 18 and 24 renders these grounds of rejection moot. Accordingly, the rejection of claims 18 and 24 under 35 U.S.C. § 103(a) is respectfully traversed.

It is respectfully submitted that the present application, as amended above, is in condition for allowance, an early notification thereof being earnestly solicited.

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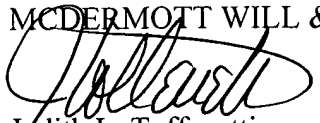
To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP



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